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L15: Entry 10 of 10 File: USPT Jun 4, 2002

DOCUMENT-IDENTIFIER: US 6399078 B1
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TITLE: Chemokine--glycosaminoglycan complexes and their use in treating or preventing receptor mediated diseases

Brief Summary Text (8):
Furthermore, later stages in tumor establishment and metastasis are also potential targets for receptor antagonist therapeutics. For example, recent studies on angiogenesis in human solid tumors have suggested that inhibiting the function of vascular endothelial growth factor (VEGF) receptors and basic fibroblast growth factor (bFGF) receptor would prove effective in blocking neovascularization in a variety of tumor types (reviewed in Toi et al. (1998) Gan To Kagaku Ryoho (Japan) 24: 2202-6). In addition, the urokinase plasminogen activator (uPA) and its receptor are essential mediators of such metastatic functions as extracellular matrix proteolysis and tumor cell migration and small molecule antagonists of the uPA receptor promise to serve as useful adjuvants in combination with existing chemotherapy strategies (Ignar, et al. (1998) Clin. Exp. Metastasis (England) 16: 9-20). Thus it is clear that receptor antagonists can inhibit the initiation and progression of cancer by blocking any of a number of processes involved in oncogenic transformation and growth. Indeed the use of receptor antagonists has even proven fruitful in the prevention of nausea and emesis (vomiting) in cancer patients undergoing chemotherapy. In particular, antagonists of the 5-hydroxytryptamine 3-receptor have proven effective toward this goal (Perez et al. (1998) Cancer J. Sci. Am. 4: 52-8).

Brief Summary Text (29):
In another embodiment, the infectious agent is a microbe which requires a specific host receptor or receptors for colonization or penetration. In preferred embodiments, the microbe is a bacterium selected from the group comprising: Helicobacter pyloris, Borelia burgdorferi, Legionella pneumophilia, Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium intracellulare, Mycobacterium kansaii, Mycobacterium gordonae, Mycobacterium leprae, Staphylococcus aureus, Neisseria gonorrhoeae, Neisseria meningitidis. Listeria monocytogenes, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus faecalis, Streptococcus bovis, Streptococcus anginosus, Streptococcus pneumoniae, pathogenic Campylobacter species, pathogenic Enterococcus species, Haemophilus influenzae, Bacillus antracis, Corynebacterium diphtheriae, Erysipelothrix rhusiopathiae, Clostridium perfringers, Clostridium tetani, Enterobacter aerogenes, Klebsiella pneumoniae, Pasturella multocida, pathogenic Bacteroides fragilis group species, Fusobacterium nucleatum, Streptobacillus moniliformis, Treponema palladium, Treponema pertenue, Leptospira, and Actinomyces isrealli. In yet other embodiments, the microbe is a fungus selected from the group comprising: Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatidis, Chlamydia trachomatis, and Candida albicans.

Detailed Description Text (36):
Still other formulations of the invention are useful to treat microbial toxin-producing infectious agents. For example, many bacterial exotoxins conform to a

bipartite structural plan composed of A and B subunits. These toxins bind to cell surfaces through the B subunit, and then the A subunit is transferred into the interior of the cell where cell injury is produced. Thus preferred receptor ligands for use in pharmaceutical formulations of the present invention would incorporate receptor ligands which bind to the B-subunit-targeted cell surface receptor and thereby prevent interaction with the microbial exotoxin. For example, cholera toxin targets the ganglioside (GM.sub.1) receptors present on the surface of human intestinal cells, resulting in the activation of adenylate cyclase which leads to secretory diarrhea. Therefore effective anti-cholera toxins would incorporate ligands capable of binding to gangliosides, which are glycolipids which contain N-acetlyneuraminic acid. Similarly the choice of receptor ligand for treating other microbial-toxin-producing infections would depend upon the offending microbe and resulting B-subunit-targeted cell surface receptor. For example, Botulinum toxin likely targets another ganglioside receptor (GD.sub.1b) and tetanus toxin may also make use of this ganglioside receptor and so ganglioside-binding ligands would again be the preferred receptor ligand component of an anti-botulism and anti-tetanus formulations. In contrast, anthrax toxin, diphtheria toxin, pertussis toxin and shiga toxin appear to target glycoprotein receptor and so preferred receptor ligands for use in treating these toxins would correspond to appropriately-chosen glycoprotein receptor binding molecules.

Detailed Description Text (85):
The receptor ligand-containing antagonist complexes may be administered to treat and or prevent the development of diseases or conditions caused by, or contributed by, the function of a cell surface receptor. Examples of such diseases and conditions include, without limitation: inflammatory diseases, e.g. septic shock, multiple organ failure, hyperacute graft or organ transplant rejection, ischemic bowel necrosis, adult respiratory distress syndrome and complement-mediated inflammatory tissue damage as well as autoimmune diseases including those resulting from or associated with the aforementioned inflammatory diseases and conditions including systemic lupus erythematosus, immune complex glomerulonephritis, and systemic vasculitis; cancer e.g., cancers due to a virus such as a tumor virus including the viruses Epstein-Barr virus, human T-cell leukemia virus (HTLV), Hepatitis B virus, and Papilloma virus, and cancers due directly or indirectly to infection by an HIV virus including HIV-1 including Kaposi's sarcoma, cancers involving the autocrine or paracrine function of a growth factor such as a fibroblast growth factor or an epidermal growth factor or a neuropeptide growth factor or interleukin 1 (IL-1) or tumor necrosis factor (TNF), also cancer involving the growth of steroid hormone-responsive tumors (e.g. breast, prostate, or testicular cancer); vascular diseases or disorders (e.g. thrombotic stroke, ischemic stroke, as well as peripheral vascular disease resulting from atherosclerotic and thrombotic processes); cardiac disorders (e.g., myocardial infarction, congestive heart failure, unstable angina and ishemic heart disease); cardiovascular system diseases and disorders (e.g. those resulting from hypertension, hypotension, cardiomyocyte hypertrophy and congestive heart failure) wound healing; limb regeneration; periodontal regeneration; aid in the acceptance of tissue transplants or bone grafts; skin aging; hair loss; muscle wasting conditions (e.g. cachexia); neurological damage or diseases or neurological or emotional conditions including Alzheimer's disease, Parkinson's disease, AIDS-related complex, cerebral palsy, or depression or neuroendocrine disorders such as hyperthyroidism or hypertension; other diseases conditions or disorders which result from aberrations or alterations of cell receptor-dependent processes including: collateral growth and remodeling of cardiac blood vessels, angiogenesis, cellular transformation through autocrine or paracrine mechanisms, chemotactic stimulation of cells (e.g. endothelial), neurite outgrowth of neuronal precursor cell types (e.g. PC12 phaeochromoctoma), maintenance of neural physiology of mature neurons, proliferation of embryonic mesenchyme and limb-bud precursor tissue, mesoderm induction and other developmental processes, stimulation of collagenase and plasminogen activator secretion, tumor vascularization, as well as tumor invasion and metastasis; or infections due to a virus (e.g. Human Immunodeficiency

Virus, an Epstein-Barr Virus, a Rhinovirus, a Poliovirus, a Rabies Virus, a Reovirus, an Influenza Virus, an Herpes Simplex Virus, an Hepatitis virus, a Togavirus, a Varicella-Zoster Virus, a Paramyxovirus, a Cytomegalovirus, a Subacute Sclerosing Panencephalitis Virus, an Adenovirus, a Poxvirus, a Reovirus, a Papovavirus, a Papillomavirus, a Polyomavirus, and a Slow virus), or a microbe, including a bacteria (e.g. Helicobacter pyloris, Borelia burgdorferi, Legionella pneumophilia, Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium intracellulare, Mycobacterium kansaii, Mycobacterium gordonae, Mycobacterium leprae, Staphylococcus aureus, Neisseria gonorrhoeae, Neisseria meningitidis, Listeria monocytogenes, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus faecalis, Streptococcus bovis, Streptococcus anginosus, Streptococcus pneumoniae, pathogenic Campylobacter species, pathogenic Enterococcus species, Haemophilus influenzae, Bacillus antracis, Corynebacterium diphtheriae, Erysipelothrix rhusiopathiae, Clostridium perfringers, Clostridium tetani, Enterobacter aerogenes, Klebsiella pneumoniae, Pasturella multocida, pathogenic Bacteroides fragilis group species, Fusobacterium nucleatum, Streptobacillus moniliformis, Treponema pallidium, Treponema pertenue, Leptospira, and Actinomyces isrealli), a fungus (e.g. Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatidis, Chlamydia trachomatis, and Candida albicans); and conditions arising from exposure to a microbial toxin including toxins produce by recognized microbial pathogens (e.g. Bacillus anthracis, a pathogenic Bordetella species, Bordetella pertussis Clostridium botulinum Clostridium tetani, Vibrio cholerae, Corynebacterium dipththeriae, Escherichia coli, Pseudomonas aeruginosa, and Shigella dysenteriae).